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Review article

Modelling human prostate cancer: Rat models

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ABSTRACT

Prostate cancer is the second most common cancer in men, affecting approximately 1.1 million men worldwide. In this way, the study of prostate cancer biopathology and the study of new potential therapies is of paramount importance. Several rat models were developed over the years to study prostate cancer, namely spontaneous models, chemically-induced models, implantation of cancer cell lines and genetically-engineered models. This manuscript aimed to provide the readers with an overview of the rat models of prostate cancer, highlighting their advantages and disadvantages, as well as, their applications.

1. Introduction

Prostate cancer is the second most common cancer in men, affecting approximately 1.1 million men worldwide. In the year 2012, prostate cancer was responsible for 307, 000 deaths, being considered the fifth leading cause of death from cancer in men [1].

Although the causes of prostate cancer are not fully understood, many risk factors have been considered for the development of this type of cancer, such as age, race, family history, diet, intrauterine conditions, hormone exposure, particularly to androgens and estrogens, and inflammation [2–5]. Since the prostate gland is an androgen-dependent tissue and consequently the prostate cancer is also androgen-dependent [2,3], the important role of androgenic hormones for prostate cancer development is well recognized [4].

Animal models have been used to study several diseases, like cancer, cerebral palsy, diabetes, Alzheimer, obesity and cardiac disease. The animal models may contribute invaluable information to better understand many aspects involved in disease development, and for the discovery and development of new pharmacological and non-pharmacological therapies (lifestyle) and preventive strategies, which may then be tested in clinical trials.

The animal models may be spontaneous, chemically-induced, transgenic/mutant animals with modifications in targeted genes, or implanted models (syngeneic or xenograft) [6–9]. An ideal animal model of human disease should be simple, not expensive and mimics the Human disease as much as possible. The rodents are commonly used in experimental research as cancer models, because they are relatively easy and cheap to maintain, their physiology and genetics are well known, they are mammals like Humans and the tumor's development is fast (all steps of carcinogenesis - initiation, promotion, progression and metastasis - may be observed) [7,9]. Despite all these advantages, the use of rodent models have some disadvantages, like the anatomic differences with humans (*e.g.* lobulated prostate in rodents *vs.* non-lobulated prostate in men), the xenograft cancer models have compromised immune systems and do not represent the behavior of naturally occurring cancer in humans, and the researchers are unable to control the level and pattern of gene expression in genetic-engineered models [10].

This review focused on rat prostate cancer models that have been established over the years for prostate cancer study, highlighting their advantages and disadvantages, as well as, their applications. We also describe the works performed in these prostate cancer models for the evaluation of several drugs and natural compounds.

2. Rat prostate: Anatomy and histology

Prostate is an accessory gland typically associated with the male reproductive tract. However, it is not exclusive of males, being also present in Mongolian gerbil female [11,12]. Prostate is found below the

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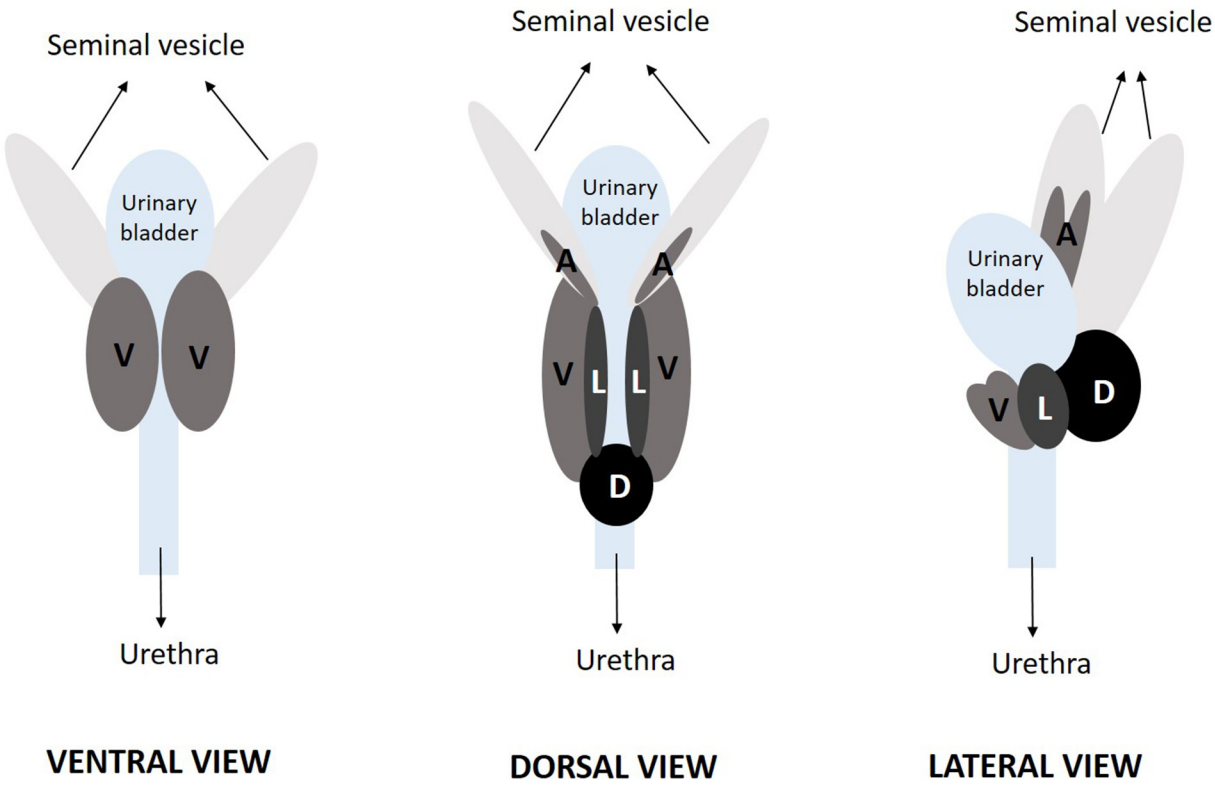

Fig. 1. Schematic representation of rat prostate. It consists of four distinct lobes according to their relative position to urinary bladder: ventral (V), lateral (L), dorsal (D) and anterior (A) lobes.

bladder in front of the rectum. Despite analogies found in prostate morphogenesis in different species, the variability of its anatomy among mammals is remarkable. While the prostate is a compact solitary structure in men and dogs, the prostate of rats and mice consists of distinct lobes. The rat prostate consists of four distinct lobes: the ventral, lateral, dorsal and anterior lobes, according to their relative position to urinary bladder [2,13] (Fig. 1). Each lobe has different morphological characteristics. The **ventral lobe**, unlike the others, does not have a human homologue, and consists of two discrete lobes ventrolateral to the urinary bladder and attached to the urethra by connective tissue; the **dorso** and **lateral lobes**, commonly referred as dorsolateral prostate, are located along the urethra, forming a macroscopic mass. The **anterior lobes** are thin tubular structures attached to the seminal vesicles [14]. The knowledge of the different rat prostate lobes is important, because the ability to develop carcinomas vary among them [2]. The man prostate is a walnut-sized gland located beneath the urinary bladder and it is just one tubule-alveolar gland [15]. Despite these anatomical differences, recent studies found similarities in the molecular mechanisms underlying prostate cancer development in rats and men, making the rat as a valid animal model to study human prostate cancer.

3. Rat as a model of prostate carcinogenesis

Despite many research projects in the field of prostate cancer are carried out using cells lines (*in vitro* studies), which allow the understanding of biological aspects related to the development of this disease, they fail to mimic the complex cellular interaction that occurs in tumor microenvironment. To overcome this limitation, researchers employed their efforts for several years on the development of animal models to study this disease.

In 1937, Moore and Melchionna were the first ones to induce prostate carcinoma in the anterior lobe of the White rat prostate through the direct injection of 1:2 benzpyrene into prostate [16]. Metastasis development was not reported in this model, being considered a model limitation. Some years later, in 1945, Dunning and colleagues, induced the development of metastasizing prostate carcinomas in albino Fisher 344 rats and black agouti Irish AxC 9935 rats [17], through the implantation of methylcholanthrene crystal into prostate. Since then, several experimental researches were conducted to discover chemical carcinogenesis with tropism for prostate tissue [18]. Highlight the N-nitrosobis (2-oxopropyl) amine (BOP) discovered in 1981 by Pour [19], *the N-Methyl-N*-nitrosourea (MNU) discovered in 1986 by Pollard [13], the 3,2′-dimethyl-4-aminobiphenyl (DMAB) discovered in 1986 by Katayana [20] and the 2-amino-1-methyl-6-phenylimidazol[4,5-*b*]pyridine (PhiP) discovered in 1997 by Shirai [21].

An adequate rat model of prostate carcinogenesis should develop androgen-sensitive adenocarcinomas in a short period of time, mimic the physiology and characteristics of man tumors, and the tumors must metastasize, preferably to bones. The tumor development should be from dorsal, lateral or anterior prostate lobes that are human homologue [18].

Concerning chemical inducers, several chemical and natural compounds may be used to assess their effect on prostate carcinogenesis. Among the agents used are: lycopene [22], dehydroepiandrosterone (DHEA) [23], fluasterone [24], quercetin [25], zinc [26], vitamin E [27], selenium [28], celecoxib [29], flutamide [30], cadmium [31], pioglitazone [32], pomegranate [33,34] and cholesterol [35].

4. Rat models of prostate carcinogenesis

Several animal models are available for the study of prostate cancer: spontaneous tumors, chemically or hormonally-induced, implantation of cancer cells and genetically engineered animals [2,36].

4.1. Spontaneous tumors

The first report of prostate spontaneous tumor was in 1963 by Dr.

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